Pulmonary rehabilitation in patients with pulmonary sarcoidosis: impact on exercise capacity and fatigue.

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Short Title: Pulmonary rehabilitation in sarcoidosis: exercise capacity and fatigue.

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Abstract

Background: There is limited evidence regarding the impact of multidisciplinary pulmonary rehabilitation (PR) on exercise capacity and fatigue in patients with pulmonary sarcoidosis. **Objectives:** The aim of this study was to evaluate the impact on exercise capacity and fatigue following PR, and to examine whether baseline fatigue was related to change in exercise capacity ($\Delta\dot{V}O_{2peak}$). **Methods:** Forty-one patients with pulmonary sarcoidosis attending a 4-week inpatient PR program were recruited to this pre-post study. Both maximal exercise capacity, defined as peak oxygen uptake ($\dot{V}O_{2peak}$) and measured with a cardiopulmonary exercise test, and fatigue, assessed with the Fatigue Assessment Scale (score 10–50 points), were measured before and after PR. **Results:** There was a statistically significant improvement in $\dot{V}O_{2peak}$ (1.2 ± 2.3 mL/kg/min, p = 0.002) and fatigue decreased significantly (-1.7 ± 3.9 points, p = 0.009) following PR. The unadjusted linear regression analyses demonstrated that age (B = -0.076, p = 0.017) and baseline fatigue (B = 0.196, p = 0.001) were predictors for change in $\dot{V}$O2peak, while in the adjusted analyses (age, sex, baseline $\dot{V}$O2peak, baseline fatigue and diffusion capacity of the lung for carbon monoxide), only baseline fatigue predicted change in $\dot{V}O_{2peak}$ following PR (B = 0.165, p = 0.026). **Conclusion:** A 4-week multidisciplinary PR program improves maximal exercise capacity and reduces fatigue in patients with pulmonary sarcoidosis. Baseline fatigue only partly predicted change in $\dot{V}O_{2peak}$ following PR.

Introduction

Sarcoidosis is one of over 200 diseases under the umbrella of interstitial lung diseases (ILDs) [1]. Any organ can be affected, but up to 90% of the affected have lung involvement [2]. Reduced exercise capacity is one of the earliest impaired physiological parameters in patients with sarcoidosis [3], whilst fatigue is the most frequent reported symptom, affecting the patients` quality of life negatively [4]. The factors affecting fatigue are not clearly identified, nor does there exist standardized assessment tools or treatment strategies [4]. Physical exercise has the potential to improve exercise capacity, while the impact on fatigue is promising but still inconclusive [5, 6]. Pulmonary rehabilitation (PR), where exercise training is a core component, is recommended as a part of the comprehensive care of patients with ILD [7]. However, recommendations of PR in ILDs are mostly based on studies with a mixed group of patients with ILD or patients with idiopathic pulmonary fibrosis [8-10]. Studies including only patients with sarcoidosis are required to make specific recommendations for PR in this sub-group of ILDs [5]. Peak oxygen uptake ($\dot{V}O_{2peak}$) is an objective and precise measure of exercise capacity [11]. An incremental cardiopulmonary exercise test (CPET) is considered to be the gold standard to be able to asses exercise capacity, develop exercise prescriptions, and evaluate the effects of exercise training and PR in patients with heart and lung disease [12]. To our knowledge, no previous studies of patients with sarcoidosis have reported effects on exercise capacity, expressed as $\Delta\dot{V}O_{2peak}$ based on a CPET following a PR program. A CPET will therefore give a more accurate picture of the baseline exercise capacity, and changes in exercise capacity following PR in patients with sarcoidosis compared to submaximal tests and indirect measurements of exercise capacity. Earlier stud shows there is a weak and inverse relationship between fatigue and $\dot{V}O_{2peak}$ in patients with sarcoidosis [13, 14], it is however not known to what extent the baseline fatigue score will affect the change in $\dot{V}O_{2peak}$ after PR. Due to the uncertainty regarding managing fatigue in relation to exercise training, combined with the high prevalence of reduced exercise capacity in sarcoidosis [15], it is clinically relevant to study whether baseline fatigue may affect the ability to improve $\dot{V}O_{2peak}$ following PR. The main aim of this study was to examine the changes in $\dot{V}O_{2peak}$ and fatigue following a multidisciplinary PR program in patients with pulmonary sarcoidosis. The secondary aim was to examine the association between baseline fatigue and change in $\dot{V}O_{2peak}$ following PR. We hypothesized that a high level of baseline fatigue was related to less improvement in $\dot{V}O_{2peak}$.

Materials and Methods

Study design and subjects

This study had a pre-post design. Fifty-nine patients (aged >18 years) with pulmonary sarcoidosis as diagnosed in accordance with guidelines [16], who were admitted to a 4-week inpatient multidisciplinary PR program (LHL Hospital Gardermoen, Norway) between April 2016 and June 2017 were eligible. Patients were excluded if they 1) had a concurrent and predominant diagnosis of another significant respiratory disorder (asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, or lung carcinoma); 2) had unstable cardiovascular disease; or 3) were unable to perform the required physical tests and follow the exercise training program due to co-morbidities (Figure 1). All patients were in a stable phase of the disease and those on medication used their standard medication. The Regional Committee for Medical and Health Research Ethics approved the study (2014/2020), and written informed consent was obtained from each study participant. The study was registered at the ClinicalTrials.gov (NCT02735161) before the first patient was included.

Pulmonary rehabilitation program

Seven different health-care disciplines contributed during the 4-weeks inpatient multidisciplinary PR program. All patients were encouraged to follow the standard activity plan consisted of two to four 45-minute educational sessions and exercise group sessions on all weekdays (Table 1). In addition to following the standard activity plan, all patients received an individually tailored resistance- and endurance training program as prescribed by a physiotherapist. The program included a high intensity endurance interval training program (4 x 3 minutes intervals on a treadmill at 85% of maximal heart rate (HR_{max})), as described in detail in a previous paper [17], and a high-intensity resistance training (4 sets of 5 repetition maximum). Both programs were prescribed to be carried out two to three times a week, with at least one weekly session being supervised such as intensities could be adjusted by the physiotherapist. All patients were seen at least once weekly by their attending physician and the patients were followed up daily by nurses. Patients were given individual appointments with a social worker, occupational therapist, clinical dietitian and psychologist as required based on initial assessments.

Table 1. Content of the multidisciplinary PR program

Type of intervention	No. of sessions
Individual exercise training	
Intervals on treadmill, 4 × 3 min	10
Resistance training, 5RM weight machines	10
Exercise training in group sessions	
Group training, "aerobics"	7
Water gymnastics	3
Outdoor walking	2
Medical yoga	2
Psychomotoric physiotherapy	2
Group education and discussions	
Coping/living with sarcoidosis (Psychologist)	5
Nutrition (Clinical dietitian)	2
Physical activity and exercise (Physiotherapist)	2
Energy conserving techniques(Occupational therapist)	2
Medication and pathology of sarcoidosis(Pulmonologist)	2
Sickness benefits, financial and social assistance (Social worker)	2
Mastery and life after PR (Nurse)	4
Total	55

Number of 45 min sessions offered during 4-week inpatient PR.
In addition, individual appointments with the therapeutic team (physician, nurse, physiotherapist, occupational therapist, psychologist, social worker and clinical dietitian)
Abbreviations: PR, Pulmonary rehabilitation; RM, Repetition maximum.

Background variables

Information about medical history was collected from the pulmonary physician's medical report the first days of the PR program, and a set of background and baseline measures were obtained. Weight and height was measured and body mass index calculated. Lung function tests: forced vital capacity (FVC), forced expiratory volume in 1 sec (FEV_1), total lung capacity (TLC), and diffusing capacity of the lung for carbon monoxide (DLCO) were performed according to international guidelines [18]. Functional capacity was assessed using the 6-minute walk test (6MWT) in accordance with standard criteria [19].

Outcome variables

Cardiorespiratory responses

All patients performed a maximal cardiopulmonary exercise test (CPET) at baseline and following 4-weeks of PR (Ganshorn Schiller CS-200/ Vyntus CPX, Switzerland). The protocol used was a stepwise, incremental treadmill test until exhaustion: rest phase was 3 minutes, work rate increased by 0.6 km/hour every two minutes up to 5.4 km/hour, thereafter by increasing the elevation from 4% to 6% and up to maximal 8%. The last step of the protocol was a further increase in speed by 0.6 km/hour every two minutes until test termination. The recovery phase was 5 minutes. Peak oxygen uptake ($\dot{V}O_{2peak}$, $ml \cdot kg^{-1} \cdot min^{-1}$), minute ventilation ($\dot{V}E$), breathing frequency (BF), oxygen pulse (O_2 pulse = O_2

/HR) and respiratory exchange ratio (RER) were recorded continuously and peak values are reported. Oxygen saturation (S_pO_2) and heart rate (HR) (Model 3150 oximeter, NONIN Medical, USA) were recorded before test start, at the end of each two minute step and upon test termination. $\dot{V}O_{2peak}$ % of predicted is based on reference values from a Norwegian population [20], and normal $\dot{V}O_{2peak}$ is defined as > 84 % of the predicted $\dot{V}O_{2peak}$ [11]. HR_{peak} % of predicted is based on the formula 220 – age. Patients were continuously monitored with 12-lead electrocardiography (Schiller CS-200, Schiller Switzerland/Custo Med GmbH, Germany). Perceived exertion, here termed as breathlessness was assessed before test start, at the end of each two minute step and upon test termination, using the Borg Category Ratio scale (Borg CR10) [21]. The scale range from 0 to 10, and patients were asked to grade their perceived breathlessness where *0* = nothing at all, *5* = strong, and *10* = very, very strong.

Fatigue

Fatigue was assessed at baseline and after 4-weeks of PR using the Fatigue Assessment Scale (FAS). FAS is validated in patients with sarcoidosis [22, 23] and consists of 10-items: five questions reflecting physical fatigue and five questions reflecting mental fatigue. The total score range is from 10 to 50 points where a score < 22 indicates no fatigue. Scores between 22 and 34 indicate mild to moderate fatigue, and scores ≥ 35 indicate severe fatigue [24]. A change in the FAS score of at least 4 points represents the minimal clinically important difference (MCID) for patients with sarcoidosis [25].

Statistical analyses

Descriptive statistics were used to characterize the study population (mean and standard deviation (SD) or number and percentage). Relevant variables ($\dot{V}O_{2peak}$ and fatigue) were tested for normal distribution by visual inspection of histograms, Q-Q plots and Shapiro Wilks test. The main statistical analyses were performed on the intention-to-treat (ITT) principle. In case of missing values, the last observation was carried forward. A paired-sample t-test was performed to detect changes in exercise capacity ($\Delta\dot{V}O_{2peak,}$ $\dot{V}O_{2post} - \dot{V}O_{2pre}$) and fatigue from baseline to after PR. Bivariate and multivariate linear regression analyses were used to examine potential predictors for change in $\dot{V}O_{2peak}$ from baseline to after 4-week PR ($\Delta\dot{V}O_{2peak}$). Investigated variables at baseline were age, sex, weight, height, FVC, FEV_1, TLC, DLCO, sarcoidosis in more than one organ, comorbidities, baseline $\dot{V}O_{2peak}$ and baseline fatigue. Variables were included in the multivariate analysis if p-value was <0.200 except for age and sex, and a backward regression models were used. Estimated regression coefficients are presented with 95 % confidence interval (CI) and *p*-values. The significance level was set at 0.05. The data analyses were performed using IBM SPSS Statistics version 22 (SPSS Inc, Chicago, IL, USA).

Results

Description of the sample

Forty-seven of the 59 patients (80%) with pulmonary sarcoidosis attending PR during the recruitment period met the inclusion criteria (Figure 1). Four declined to participate and 43 patients were included. Two patients were excluded after one week and relocated to other hospitals for further medical investigations. A total of 41 patients completed the 4-week PR program. Missing values were CPET (n = 4), and FAS questionnaire (n = 3) post PR.

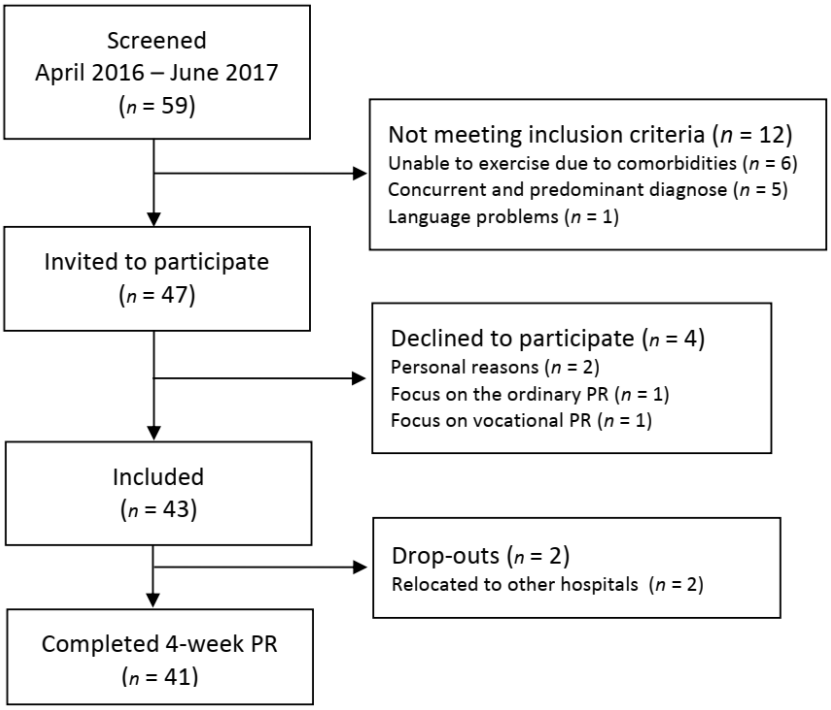

Figure 1. Flowchart

The sample was evenly divided between female and male, with normal to mildly impaired lung function and reduced maximal exercise capacity (Table 2). Thirty-one of the 41 patients (76%) failed to reach 84% of their predicted $\dot{V}O_{2peak}$. The majority of the patients (80.5%) had mild to moderate fatigue with a FAS score between 22-34 points, 14.6% had severe fatigue with a FAS score > 35 points, and 4.9% had a FAS score < 22 points. None of the patients required oxygen supplementation during exercise.

Table 2. Baseline characteristics, *n* = 41.

Characteristic	Mean ± SD	*n* (%)
Age, years	53 ± 11	
Sex, female		21 (51)
BMI, kg/m^2	30 ± 6	
FVC, % pred.	93 ± 21	
FEV_1, % pred.	82 ± 22	
TLC, % pred.	93 ± 18	
DLCO, % pred.	76 ± 16	
$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1}	24.6 ± 6.8	
$\dot{V}O_{2peak}$, % pred.	72 ± 19	
6MWD, m	578 ± 107	
Fatigue, FAS 10-50 points	29.8 ± 5.8	
Medication		
Prednisolon		11 (27)
Methotrexate		6 (15)

Data are presented as mean (SD) or n (%). BMI, body mass index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; $\dot{V}O_{2peak}$, peak oxygen uptake; 6MWD, 6-minute walk distance; FAS, fatigue assessment scale.

Primary Outcomes

There was a statistically significant improvement in maximal exercise capacity, $\dot{V}O_{2peak}$ of 1.2 ± 2.3 mL·kg^{-1}·min^{-1} (p = 0.002) from baseline to after PR. Participants were able to perform all exercise tests, and reached the same peak values for SpO_2, HR, RER and blood lactate. Concurrently they showed a statistically significant longer exercise time (p = 0.007) and higher ventilation (p = 0.033), in addition to a significantly lower perceived breathlessness (p = 0.006) (Table 3). The fatigue scores decreased by 1.7 ± 3.9 points (p = 0.009) (Table 3). An improvement in fatigue, which is observed by a reduction in FAS by ≥ 4 points was observed in 32% of the patients, 61% reported an unchanged fatigue (between 3 and -3 points), and 7% reported a worsening in fatigue (≥ 4 points).

Table 3. Fatigue and maximal values from CPET at baseline and after 4-week PR, *n* = 41

Variables	Baseline	After PR	*p*-value
Fatigue, FAS 10-50 points	29.8 ± 5.8	28.1 ± 5.8	0.009
CPET measure			
Test time, min:sec	12:29 ± 3:16	13:22 ± 3:01	0.007
Breathlessness peak, Borg CR10	8.5 ± 2	7.7 ± 2	0.006
S_pO_2, %	92 ± 5	92 ± 4	0.247
HR_{peak}, bpm	153 ± 20	152 ± 19	0.231
HR_{peak} pred, %	91.3 ± 12	91.0 ± 10	0.717
Bodyweight, kg	88.7 ± 17.6	88.0 ± 17.3	0.001
$\dot{V}O_{2peak}$, L·min^{-1}	2.15 ± 0.6	2.24 ± 0.7	0.009
$\dot{V}O_{2peak}$, mL·kg^{-1}·min^{-1}	24.6 ± 6.8	25.8 ± 7.2	0.002
$\dot{V}O_{2peak}$ pred, %	72 ± 19	75 ± 20	0.002
$\dot{V}E_{peak}$, L·min^{-1}	75.4 ± 25	79.3 ± 27	0.033
BF_{peak}, breaths·min^{-1}	37 ± 7	39 ± 8	0.016
RER_{peak}	1.05 ± 0.11	1.05 ± 0.10	0.746
O_2 pulse, mL·beat^{-1}	14.0 ± 3.2	14.7 ± 3.4	0.001
Lactate peak, mmol·L^{-1}	7.9 ± 3.4	8.0 ± 3.2	0.891

Data presented as mean ± SD. CPET, cardiopulmonary exercise test; PR, Pulmonary rehabilitation; FAS, fatigue assessment scale; S_pO_2, oxygen saturation; HR, heart rate; VO_{2peak}, peak oxygen uptake; VE, minute ventilation; BF, breathing frequency; RER, respiratory exchange ratio; O_2 pulse, oxygen pulse.

Secondary Outcomes

No correlation was observed between baseline fatigue and baseline $\dot{V}O_{2peak}$ (r = 0.078, p = 0.630), while there was a statistically significant correlation between baseline fatigue and $\Delta\dot{V}O_{2peak}$ (r = 0.49, p = 0.001), where higher baseline fatigue score was associated with a larger improvement in $\dot{V}O_{2peak}$ following 4-weeks of PR (Figure 2). The unadjusted regression analysis demonstrated that age (B = -0.076, p = 0.017) and baseline fatigue (B = 0.196, p = 0.001) were predictors for change in $\dot{V}O_{2peak}$ from baseline to after PR. A lower age was associated with a larger change in $\dot{V}O_{2peak}$, and a higher baseline fatigue score was associated with a larger improvement in $\dot{V}O_{2peak}$. While in the adjusted analysis only baseline fatigue predicted changes in $\dot{V}O_{2peak}$ following PR (B = 0.165, p = 0.026), and indicated that baseline fatigue explained 11% of the change in $\dot{V}O_{2peak}$ from baseline to after PR

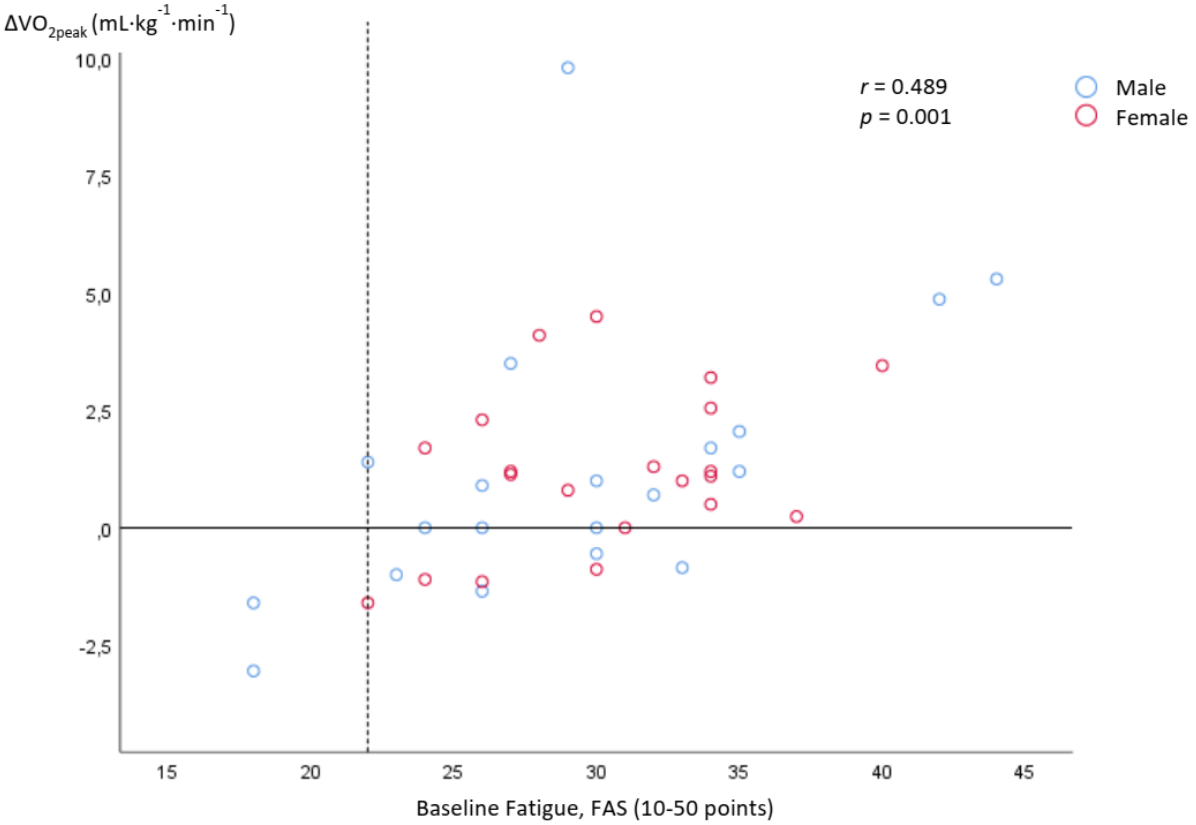

Fig. 2. Relationship between ΔV̇O2peak and baseline fatigue.
ΔV̇O2peak, change in peak oxygen uptake from pre to post PR; FAS, Fatigue Assessment Scale; Dotted vertical line, cut-off for FAS fatigue (22 points).

Table 4. The relationship between the $\Delta\dot{V}O_{2peak}$ and potential explanatory variables

	Unadjusted			Adjusted			
Variable	B	St.B[1]	*p*-value	B	St.B[1]	95% CI	*p*-value
ΔVO_{2peak} ($ml \cdot kg^{-1} \cdot min^{-1}$)							
Fatigue baseline	0.196	0.489	0.001	0.165	0.410	0.021 – 0.309	0.026
Age	- 0.076	- 0.371	0.017	- 0.029	- 0.142	- 0.105 – 0.047	0.443
Sex	0.016	0.003	0.983	- 0.145	0.849	- 1.678 – 1.389	0.849
Weight	0.003	0.023	0.884				
Height	- 0.048	- 0.183	0.251				
FVC	0.184	0.073	0.650				
FEV_1	0.488	0.174	0.277				
TLC	- 0.041	- 0.025	0.879				
DLCO	0.204	0.146	0.361	0.184	0.132	- 0.306 – 0.674	0.450
$\dot{V}O_{2peak}$ baseline	0.008	0.023	0.887	- 0.037	- 0.106	- 0.152 – 0.079	0.526
Sarcoidosis > 1 organ	0.552	0.103	0.522				
Comorbidities	- 0.760	- 0.156	0.329				

95 % confidence interval (CI) examined by linear regression in bivariate and multivariate analysis.
FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 sec; TLC, total lung capacity; DLCO, diffusing capacity of the lung for carbon monoxide; $\dot{V}O_{2peak}$, peak oxygen uptake; [1] St.B, standardised beta.

Discussion

Four weeks of multidisciplinary PR led to statistically significant improvements in $\dot{V}O_{2peak}$ and significantly reduction in fatigue in patients with pulmonary sarcoidosis. Baseline fatigue score was a predictor of change in $\dot{V}O_{2peak}$ from baseline to after PR. However, only 11% of the improvement in $\dot{V}O_{2peak}$ could be explained by the baseline fatigue. An interesting and promising observation was that a high baseline fatigue score was associated with a larger improvement in $\dot{V}O_{2peak}$ following PR.

Impaired exercise capacity, expressed as peak oxygen uptake ($\dot{V}O_{2peak}$), has been reported to be one of the earliest impaired physiological parameters in patients with sarcoidosis, regardless of disease severity [3,26]. This was confirmed in our sample where lung function tests were more or less normal whilst they reached only 72% of predicted $\dot{V}O_{2peak}$ at baseline, which is below the lower limit for what is defined as normal (> 84% of predicted $\dot{V}O_{2peak}$) [11]. It is well documented that PR increase exercise capacity in patients with COPD, and emerging evidence also supports this in patients with ILD [7]. However, compelling improvements in exercise capacity was only observed in functional exercise capacity, measured by the 6MWT, following PR in patients with ILD, whilst only small improvements in maximal exercise capacity, measured as $\dot{V}O_{2peak}$ was reported [8]. The current study demonstrates that a 4-week inpatient PR program resulted in statistically significant improvements in $\dot{V}O_{2peak}$ (1.2 mL·kg-1·min-1). This is in line with the review by Dowman, which reported a mean difference of 1.24 mL·kg-1·min-1 after 8-12 weeks of PR patients with ILD [8]. The result from the review of PR in ILD may not be representative for patients with sarcoidosis as the

majority of the participants included had idiopathic pulmonary fibrosis [8], which is associated with a poorer prognosis compared to sarcoidosis [27]. This was clearly demonstrated by the difference in baseline $\dot{V}O_{2peak}$ of 13.6 mL·kg-1·min-1 in the patients with idiopathic pulmonary fibrosis [28], compared to 24.6 mL·kg-1·min-1 in our sample of patients with sarcoidosis. However, the baseline $\dot{V}O_{2peak}$ –values in our study was consistent with the baseline $\dot{V}O_{2peak}$ of 25.4 mL·kg-1·min-1 assessed in a study by Stookappe et al. [29], including only patients with sarcoidosis. This gives a clear picture of the heterogeneity of the pathophysiology, initial fitness levels and exercise limitations amongst sub-groups of ILDs, which makes it difficult to compare studies including a mixed group of ILDs. The improvement of 1.2 mL·kg-1·min-1 in our study, was however less than the improvements in the study by Stookappe of 2.3 mL·kg-1·min-1 [29]. We assume the difference in improvement was due to the difference in content and duration between the two studies. The results in our study was assessed following a 4-week multidisciplinary PR program where the patients might have several goals in addition to improve exercise capacity, whilst the results by Strookappe was achieved following a 12-week exercise training program. Due to the limited studies evaluating the impact on $\dot{V}O_{2peak}$ following a multidisciplinary PR program in a sample of patients with sarcoidosis, this study may give valuable information which is important to be able to compare effects from PR in this sub-group of ILDs.

This study also demonstrates the advantages of using a CPET to evaluate changes in exercise capacity following a PR program. In addition to improved $\dot{V}O_{2peak}$, the results demonstrated that the patients were able to perform the maximal exercise tests, as typical help-criteria to determine the true VO_{2max} were reached in both CPETs [30]. The HRpeak of 91% of predicted was within the accepted recommendations (HR_{peak} > 90 % of predicted) [11], as well as the RER value of 1.05 (≥ 1.05) and blood lactate concentration of 8 mmol/l (≥5.0 in female and ≥ 6.0 mmol/l in male) [30]. Improved exercise capacity following PR was also proven by the significantly longer exercise time and higher ventilation. Interestingly, the Borg score of breathlessness was significantly reduced following PR, suggesting the participants` perceived the increased effort on the second CPET as less strenuous than at baseline. The improvement in $\dot{V}O_{2peak}$ could be influenced by weight loss. Even though there was a significant reduction in bodyweight of 0.7 kg following PR, the improvement in $\dot{V}O_{2peak}$ in absolute values (L·min-1) remained significant. Thus, we assume that the improvement in $\dot{V}O_{2peak}$ following PR in this study were mainly due to physiological adaptations as a response to exercise training, which is a promising improvement due to the short duration of 4 weeks of exercise training.

In addition to impaired $\dot{V}O_{2peak}$, fatigue is one of the most commonly reported and debilitating symptoms in sarcoidosis, where convincing treatment strategies are still lacking [6]. An important treatment goal has therefore been to improve exercise capacity without worsening

fatigue, or at best to also reduce the level of fatigue [5]. Fatigue is more or less absent in other ILDs than sarcoidosis, therefore has fatigue not been reported as an outcome in reviews of PR in ILD [8-10]. The current study show the patients expressed less fatigue following PR with a statistically significant decrease of 1.7 points on the FAS. Thirty-two percent of the patients had a reduction in fatigue ≥ 4 points, which is the minimal clinically important difference of fatigue on the FAS. Our findings was similar to what was observed in the study by Lingner et al. [31], where 39% of the patients reported a reduction in fatigue ≥ 4 points after 3 weeks of PR. An assumption is that the duration of 4 weeks in this study, and 3 weeks in the study of Lingner and colleagues, was too short to affect the ability to reduce fatigue even more. However, similar result was seen following a 13 weeks exercise training program, where 33 % of the patients reported a reduction in fatigue ≥ 4 points [32]. Furthermore, the complexity of fatigue in regards to exercise training was also demonstrated in a randomized control study in 90 patients with sarcoidosis [29], where 74.4% of the patients in the exercise group of 49 patients reduced fatigue by ≥ 4 points, but also 48.7% of the 41 patients in the non-exercising control group showed a clinically important reduction in fatigue after 12 weeks [29]. Even if all the fours abovementioned studies reported statistically significant reduction in fatigue, it also reveal that a substantial numbers of the patients do not achieve improvement in fatigue following PR or exercise training programs. Nevertheless, our study is promising in relation to avoid aggravation of fatigue following PR. The majority of the patients expressed an improved (32%) or unchanged (61%) fatigue score following PR, and only 7% of the patients expressed a worsening in fatigue. The present results are in keeping with a previous study examining the impact of a 13-week exercise training program in fatigued patients with sarcoidosis, where 33.3% of the patients reported a reduction in FAS fatigue of ≥ 4 points, 61.1% unchanged fatigue, and 5.6% a worsening of fatigue ≥ 4 points [32]. Because few studies have reported the number of patients with unchanged or a worsened fatigue following PR or exercise training, the results of Marcellis and this study provide important evidence that PR and exercise training appears to be well tolerated in patients with sarcoidosis-related fatigue.

The prevalence of fatigued patients (FAS ≥ 22 points) in our sample was high (95% of the patients), as was reduced exercise capacity of < 84% of predicted $\dot{V}O_{2peak}$ (76% of the patients). There was no correlation between baseline fatigue and baseline $\dot{V}O_{2peak}$ in our study, but several previous descriptive studies have reported an inverse relationship where a high level of fatigue correlated with reduced exercise capacity (both 6MWD and $\dot{V}O_{2peak}$) [13, 14, 33, 34]. We therefore hypothesized that the baseline fatigue level might influence the ability to improve $\dot{V}O_{2peak}$ following PR, where we assumed a high level of fatigue at baseline would lead to less improvement in $\dot{V}O_{2peak}$. This is a clinical relevant issue often asked by the patients and health care professionals. The current study showed a

medium correlation between baseline fatigue and change in $\dot{V}O_{2peak}$. Surprisingly, the correlation was positive, where a high level of fatigue at baseline was related to larger improvement in $\dot{V}O_{2peak}$ following PR (Figure 2). Baseline fatigue was also the only potential variable that could predict change in $\dot{V}O_{2peak}$. Nevertheless, only 11% of the change in $\dot{V}O_{2peak}$ was explained by baseline fatigue. These findings might be a motivational factor for patients suffering from fatigue attending PR. However, caution should be used when interpreting these findings, due to low number of patients and the pre-post design without a control group in out study. Future studies with a more rigorous design (randomized controlled trials) are needed to confirm our results.

Strengths and limitations

A methodological strength was that maximal exercise capacity was measured by direct assessment of $\dot{V}O_{2peak}$ during a CPET, where the reference values to evaluate a maximal test of HR, lactate and RER were reached and clearly indicated that $\dot{V}O_{2peak}$ was achieved. There were no drop-outs from the 4-week PR program, suggesting that our PR program including high-intensity protocol may be a feasible exercise strategy in a PR program for patients with sarcoidosis. A limitation of this study is that we did not record all the activity the patients performed during the 4-week PR program. The patients attended an inpatient setting where the fitness room was open 24 hours a day for individual exercising, hence there might have been differences in the frequency the exercise was performed.

Conclusion

This pre-post study showed that multidisciplinary PR is safe and beneficial in improving exercise capacity and reducing fatigue in patients with pulmonary sarcoidosis. Baseline fatigue was partly related to change in $\dot{V}O_{2peak}$ following PR, where a higher level of baseline fatigue was associated with a larger improvement in $\dot{V}O_{2peak}$ following PR.

Acknowledgement

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Statement of Ethics

The Regional Committee for Medical and Health Research Ethics approved the study (2014/2020),

and written informed consent was obtained from each study participant. The study was registered at the ClinicalTrials.gov (NCT02735161) before the first patient was included.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Conceptualization, A.G., M.A.S. and A.E.; Methodology, A.G., N.K.V., L.M.O., M.A.S., and A.E.; Validation, A.G., N.K.V., L.M.O., M.A.S., and A.E.; Formal analysis, A.G., N.K.V., L.M.O., M.A.S., and A.E.; Investigation, A.G.; Data curation, A.G. and A.E.; Writing—original draft preparation, A.G. and A.E.; Writing—review and editing: A.G., N.K.V., L.M.O., M.A.S., and A.E.; Visualization, A.G.; Supervision: A.E., N.K.V., L.M.O. and M.A.S.; Project administration, A.G. and A.E.; Funding acquisition: A.G. and A.E.

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Figure Legends

Fig. 1. Flowchart of recruitment, inclusion and drop-outs. PR, pulmonary rehabilitation.

Fig. 2. Relationship between ΔV̇O2peak and baseline fatigue.
ΔV̇O2peak, change in peak oxygen uptake from pre to post PR; FAS, Fatigue Assessment Scale; Dotted vertical line, cut-off for FAS fatigue (22 points).